

REMARKS

As a preliminary matter, Applicants' representative and Assignee's representative thank the Examiner for courtesies extended during the telephonic interview of January 11, 2007. During the interview, the rejections of record were discussed and possible means for overcoming the rejections. The Examiner clarified that the references being cited in support of the rejection under 35 U.S.C. § 102(a) are U.S. Patent No. 6,605,617, U.S. Patent Application Publication No. 2002/0107392, and WO 2002/22598.

By the present communication, claims 42 and 52 are currently amended, claims 1-41, 44-51, and 53-68 are cancelled without prejudice, and new claims 69-92 are added. The amended and new claim language finds support throughout the application and claims as filed, including but not limited to claim 42 and paragraphs 288, 289, 293, 294, 295, 296, 297, 301, 305, 306, 307, 308, Example 166, claim 43, paragraphs 11, 12, 13, 77 and 753. No new matter has been introduced by these amendments. Claims 42, 43, 52, and 69-92 are pending.

In view of the foregoing amendments and the following remarks, reconsideration of the application is respectfully requested.

I. Rejection Under 35 U.S.C. § 112, First Paragraph

A. Written Description

Claims 42, 43 and 52 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The rejection is summarized as: "The instant specification does not adequately describe the nexus between the modulation of the specific tyrosine kinases (i.e. c-Kit among others[]) and a useful treatment of a disease/condition." Applicants respectfully traverse this rejection for the reasons provided below.

Applicants respectfully submit that, independent claim 42 as amended meets the written description requirement because each kinase plays a critical role in one or more disorders. Each

of the tyrosine kinases are known to mediate or otherwise contribute to a variety of disorders, including certain cancers as evidenced by the discussion set forth in the application at, e.g., paragraphs 9-14. Moreover, each of these kinases was well known at the time of filing to be mediators of various disorders such as cancer as evidenced by the articles listed in Table 1 below. The Examiner has only to peruse the scientific literature to discover hundreds of peer-reviewed articles on the link between the recited tyrosine kinases and various cancers and other disorders. Thus, contrary to the assertion in the Office Action, nexus exists for each recited kinase and many disorders, especially cancer. Given such nexus, the skilled artisan would readily understand that Applicants had possession of the claimed invention at the time of filing. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 42, 43, and 52 for lack of written description.

Applicants also submit that new claims 69-92 are supported throughout their scope by the application as filed. New claims 69-82 depend from claim 42 and possess written description for the same reasons set forth above. New independent claims 83 and 89 recite, respectively, methods of treating cancer mediated by the recited tyrosine kinases and methods of treating specific cancers. These cancers are mediated by the very kinases recited in claims 42 and 83 and which are discussed above. Moreover, the working examples (paragraphs 723-769) demonstrate that compounds of the claimed invention both inhibit the recited kinases and possess *in vivo* anti-cancer activity. In view of this level of disclosure, it is clear that Applicants therefore possessed the subject matter of claims 83, 89, and claims depending therefrom, at the time of filing the application. As such, Applicants submit that new claims 69-92 comply with the written description requirement of 35 U.S.C. § 112, 1st paragraph.

B. Enablement

Claims 42, 43 and 52 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. In support of the rejection, a Wands analysis is set forth in the Office Action on pages 4-8. Applicants respectfully traverse this rejection.

Applicants respectfully submit that an analysis of the Wands factors show that the claimed invention is fully enabled. For example, the breadth of the claims and nature of the invention support enablement of the claimed invention. Contrary to the assertions in the Office Action, the claims are not “drawn to the treatment of any and all diseases mediated by the tyrosine kinase receptor with the compounds.” As amended, independent claim 42 recites a method of inhibiting a tyrosine kinase selected from a limited number of such kinases. Claims 43, 52 and new claims 69-82 further define the compounds being used in the method. New independent claim 83 recites a method of treating cancer mediated by the same kinases; new dependent claims 84-88 recite specific cancers. New claims 89-92 also recite methods of treating specific cancers. Thus, the claims are not drawn to treatment of any and all diseases mediated by tyrosine kinase receptors, and therefore are not unreasonably broad as implied in the Office Action.

The state of the art and the level of predictability in the art also support enablement of the claimed methods. In the Office Action, it is asserted with regard to the state of the art that “[t]here is no absolute predictability even in view of the seemingly high level of skill in the art.” Office Action, page 5. It is further asserted that “the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity,” and “the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects of all diseases, whether or not the modulation of the tyrosine kinase c-Kit or other specific tyrosine kinase receptors would make a difference in the disease.” Applicants respectfully submit that the Action overstates the unpredictability of the claimed subject matter and fails to acknowledge the extensive evidence showing the link between the inhibition of the recited tyrosine kinases, such as c-Kit and p60src, and treatment of cancer.

Applicants have submitted (in IDSes) and submit herewith numerous articles establishing the role of tyrosine kinases in cancer at the time the application was filed. These articles and their findings are summarized in Table 1 below for the convenience of the Examiner.

TABLE 1

KINASE	REFERENCE	FINDINGS
FLT-3	Levis, M., <i>et al.</i> , "A FLT3-targeted tyrosine kinase inhibitor is cytotoxic to leukemia cells in vitro and in vivo," Blood 99, 11; 2002 (submitted in 11/14/2003 IDS)	<p>FLT-3 is a receptor tyrosine kinase "aberrantly expressed on malignant cells in a majority of patients with acute myelogenous leukemia (AML) cells." (p. 3885)</p> <p>"We describe here the identification and characterization of the indolecarbazole derivative CEP-701 as a FLT3 inhibitor. This drug potently and selectively inhibits autophosphorylation of wild-type and constitutively activated mutant FLT3 in vitro in FLT3/ITD-transfected cells and in human FLT3-expressing myeloid leukemia-derived cell lines. We demonstrate that CEP-701 induces a cytotoxic effect on cells in a dose-responsive fashion that parallels the inhibition of FLT3. STAT5 and ERK1/2, downstream targets of FLT3 in the signaling pathway, are inhibited in response to FLT3 inhibition. In primary leukemia blasts from AML patients harboring FLT3/ITD mutations, FLT3 is also inhibited, with an associated cytotoxic response. Finally, using a mouse model of FLT3/ITD leukemia, we demonstrated that the drug inhibits FLT3 phosphorylation in vivo and prolongs survival." (Abstract)</p>
c-Kit, Bcr-Abl	Heinrich, M. C. et al., "Inhibition of KIT Tyrosine Kinase Activity: A Novel Molecular Approach to the Treatment of KIT-Positive Malignancies," J. Clin. Onc. 2002, 20, 1692-1703, 2002 (review article) (submitted in 11/14/2003 IDS);	<p>C-kit expression has been documented in a number of cancers including mast cell leukemia, germ cell tumors, small-cell lung carcinoma, gastrointestinal stromal tumors, acute myelogenous leukemia (AML), neuroblastoma, melanoma, ovarian carcinoma, breast carcinoma. (pp. 1692-1693)</p> <p>"The fact that STI571 (imatinib mesylate; Gleevec; Novartis pharmaceuticals, East Hanover, NJ) is imperfectly selective (Table 2) has been exploited in the successful treatment of two very different cancers. In the case of chronic myelogenous leukemia (CML), the drug inhibits kinase activity of the BCR-ABL fusion gene product, whereas in GISTs, the drug inhibits KIT tyrosine kinase." (p. 1694)</p>
c-Kit	Smolich, B. D. et al. "The antiangiogenic protein kinase inhibitors SU5416 and SU6668 inhibit the SCF receptor (c-kit) in a human myeloid leukemia cell line and in acute myeloid leukemia blasts," Blood, 97, 5; 1413-1421 (submitted in 11/14/2003 IDS)	<p>"SU5416 and SU6668 are small-molecule indolinone RTK inhibitors currently being evaluated as antiangiogenic agents in clinical trials in patients with advanced malignancies." (p. 1418)</p> <p>"The results of the studies described here show that both SU5416 and SU6668 inhibit biochemical and biologic functions of c-kit in MO7E cells, a human myeloid leukemia</p>

		cell line that expresses c-kit. At the biochemical level, both compounds inhibit ligand-induced phosphorylation of the receptor and ERK1/2 in MO7E cells and in freshly isolated c-kit+ blasts from AML, T-ALL, and CML patients. Cell proliferation, previously shown to be a downstream biologic effect of receptor stimulation and phosphorylation in MO7E cells, is also inhibited by SU5416 and SU6668 treatment.” (<i>Id.</i>)
p60src	Susa, M., <i>et al.</i> , “Src inhibitors: drugs for the treatment of osteoporosis, cancer or both?” Trends Pharmacol Sci. 2000 Dec;21(12):489-95;	“Src was one of the first proto-oncogenes to be identified and is a prototype of non-receptor type tyrosine kinases. At the cellular level, it is well established that Src plays an important role in proliferation, and adhesion and motility. In addition, recent data indicate an involvement of Src in cell survival and intracellular trafficking in various specialized cell types. These new findings suggest that Src inhibitors might have therapeutic value in the suppression of tumor growth [and] tumor angiogenesis.” (Abstract)
FGFR3	Chesi <i>et al.</i> “Activated fibroblast growth factor receptor 3 is an oncogene that contributes to tumor progression in multiple myeloma,” Blood 2001 97 729-736 (submitted in 11/14/2003 IDS)	“FGFR3 is deregulated due to a t(4;14) translocation in a subset of multiple myeloma (MM) patients. “It is shown that activated FGFR4—when expressed at levels similar to those seen in t(4;14) myeloma—is an oncogene that acts through the MAP kinase pathway to transform NIH 3T3 cells, which can then generate tumors in nude mice. Thus, FGFR3, when overexpressed in MM, may be not only oncogenic when stimulated by FGF ligands in the bone marrow microenvironment, but is also a target for activating mutations that enable FGFR3 to play a ras-like role in tumor progression.” (Abstract)
Fyn	Berwanger, B. <i>et al.</i> , “Loss of a FYN-regulated differentiation and growth arrest pathway in advanced stage neuroblastoma,” Cancer Cell. 2002 Nov;2(5):377-86;	“We now identify signal transduction through the nonreceptor tyrosine kinase Fyn as one pathway that controls neuroblastoma development in both <i>MYCN</i> amplified and nonamplified tumors. This conclusion is based on four lines of evidence. First, array analysis identifies multiple genes that encode proteins, which are functionally linked to <i>FYN</i> , as a group of genes coordinately downregulated in advanced stage tumors. Second, Western blotting and kinase assays show that Fyn expression and kinase assays show that Fyn expression and kinase activity is strongly correlated with tumor stage. Third, expression levels of Fyn predicts prognosis in neuroblastoma. Fourth, active Fyn kinase induces cell cycle arrest and differentiation in cultured neuroblastoma cells.” (Page 383)
Lck	Majolini, M.B. <i>et al.</i> “Dysregulation of the protein tyrosine kinase LCK in lymphoproliferative disorders and in other neoplasias,” Leuk Lymphoma.	“The Oncogenic potential of Lck has been firmly established experimentally. Dysregulation of Lck expression or activity in human T-cell leukemias, as well as ectopic Lck expression in other cancers supports a causal role for Lck in some neoplastic pathologies (Table I).”

	1999 Oct;35(3-4):245-54.	(Page 252)
PDGFR α , PDGFR β , c-Abl, c-Kit	Pietras, K. et L., "PDGF receptors as cancer drug targets," <i>Cancer Cell</i> , 2003, 3, 439-443.	"Glivec represents a kinase inhibitor for which there is already some clinical experience; in addition to PDGF α - and β -receptors, Glivec also inhibits Kit, Abl, and Arg tyrosine kinases. It is used in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors (GIST), characterized by overactivity of Abl and Kit, respectively, and has shown rather mild side effects." (Page 439; references omitted)
Tie-2	Siemester, G, <i>et al.</i> , "Two independent mechanisms essential for tumor angiogenesis: Inhibition of human melanoma xenograft growth by interfering with either the vascular endothelial growth factor receptor pathway or the Tie-2 pathway," <i>Cancer Res.</i> 1999, 59 3185-3191.	"In summary, we have shown that, in the A375v human melanoma xenograft model, tumor angiogenesis and tumor growth was inhibited by blockade of either the VEGF receptor pathway or the Tie-2 pathway. The observation that the blockade of a single angiogenic growth factor pathway in the presence of other angiogenic growth factors was sufficient to inhibit xenograft tumor growth suggests that using antiangiogenic drugs that interfere with either the VEGF receptor pathway or the Tie-2 pathway would be therapeutically successful. Furthermore, one would expect additive effects on tumor growth by simultaneous interference with both pathways." (p. 3190)
VEGFR3	Valtola, R., <i>et al.</i> "VEGFR-3 and its ligand VEGF-C are associated with angiogenesis in breast cancer," <i>Am J Pathol.</i> 1999 May; 154(5):1381-90.	"We conclude that the number of VEGFR-3 positive vessels is elevated in breast cancer. Part of the VEGFR-3 positive vessels are angiogenic blood vessels with up-regulated expression of VEGFR-3 in the endothelial cells. However, a part of the VEGFR-3 positive structures appear to be lymphatic vessels, although we found no evidence that lymphangiogenesis occurs in breast cancers. The presence of VEGF-C in intraductal carcinoma cells as well as the VEGFR-3 positive capillaries surrounding the affected ducts suggest that VEGF-C secreted by the cancer cells acts predominantly as an angiogenic growth factor, but it could also affect the lymphatic vessels during tumor metastasis into the axillary lymph nodes." (p. 1389)

Collectively, the articles show that the subject matter of the claims is not highly unpredictable as asserted in the Office Action, but is amenable to routine experimentation. In particular, the references establish that not only was the role of each tyrosine kinase such as c-Kit well-known at the time the present application was filed, but this role was being exploited *in vivo* with RTK inhibitors such as Glivec (which was FDA approved at the time the present application was filed) and SU11248, among others. See Pietras, et al. *Cancer Cell*, 2003, 3, 439-443. Thus,

the art shows a high degree of correlation between *in vitro* and *in vivo* results. It is unnecessary for Applicants to show absolute predictability with regard to the claimed subject matter, but merely that routine experimentation by the skilled artisan is necessary. The articles in Table 1, clearly establish the nexus between inhibition of receptor tyrosine kinases such as c-Kit and anti-angiogenic and anti-cancer effects observed in *in vivo* models and in the clinic.

The amount of direction provided and the existence of working examples in the application further support enablement of the claimed subject matter. As amended, claim 42 recites a method of inhibiting selected tyrosine kinases with the claimed compounds, and new claims 83 and 89 are focused on the treatment of very specific cancers. The working examples are highly relevant to this subject matter, showing that Applicants synthesized over 1400 compounds and found significant *in vitro* activity with respect to each of the recited kinases and significant *in vivo* activity with respect to numerous cancer models. As noted in the discussion of the state of the art above, inhibition of these kinases correlates with anti-cancer activity in *in vivo* models and in the clinic. Thus, the working examples and guidance provided in the application directly support the claimed methods. In addition, Applicants have amassed extensive evidence confirming the anti-angiogenic and anti-cancer effects of compounds of structure I, particularly the compound of Example 166, the single compound expressly recited in claims 43, 84, and 92. A summary of the working examples and confirmatory evidence of how to use the claimed invention is set forth below for the convenience of the Examiner.

Applicants respectfully direct the Examiner's attention to the *in vitro* tyrosine kinase assay procedures described on pages 423-427 of the specification in paragraphs 723-729. There the assay procedures are described in depth and with sufficient detail to enable one skilled in the art to conduct such assays and assess the inhibitory potency of various compounds of structure I. The over 1400 compounds synthesized by Applicant are set forth as Examples 1-1457 (pp. 274-421 of the specification and including Tables 1-5) and are commensurate in scope with the claimed compound of structure I. Paragraph 729 specifically states that "each of the compounds

produced in the Examples was synthesized and assayed using the procedures described above.”

The specification goes on to state:

The majority of the exemplary compounds displayed an IC₅₀ value of less than 10 μM with respect to VEGFR1, VEGFR2, VEGFR3, FGFR1, CHK1, Cdc2, GSK-3, NEK-2, Cdk2, Cdk4, MEK1, NEK-2, CHK2, CK1ε, Raf, Fyn, Lck, Rsk2, PAR-1, c-Kit, c-ABL, p60src, FGFR3, FLT-3, PDGFRα, and PDGFRβ. In addition, many of the exemplary compounds exhibited IC₅₀ values in the nM range and show potent activity with respect to VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR3, c-Kit, c-ABL, FLT-3, CHK1, Cdc2, GSK-3, NEK-2, Cdk2, MEK1, NEK-2, CHK2, Fyn, Lck, Rsk2, PAR-1, PDGFRα, and PDGFRβ with IC₅₀ values of less than 1 μM.

Thus, each of the numerous example compounds were prepared and the majority assayed and found to display inhibitory activity with respect to the recited kinases: VEGFR3, Fyn, Lck, c-Kit, c-ABL, p60src, FGFR3, FLT-3, PDGFRα, and PDGFRβ.

In addition the present application discloses copious experimental data regarding *in vivo* and *in vitro* activity of the compound of Example 166, 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one (hereinafter compound 166), in paragraphs 751-767 on pages 431-439. See also Figures 1-13 of the application. Notably, claims 43, 83 and 89 are specifically directed to methods that include the use of compound 166. As set forth in paragraph 752 of the application, the antiproliferative activity of compound 166 was assessed in 27 different cancer and primary cell lines (see Table 6) and displayed EC₅₀ values of less than 10 μM in 26 out of the 27 cell lines tested and displayed an EC₅₀ value of 10 μM for the 27th cell line tested. Of further note, the vast majority of the cancer cell lines set forth in Table 6 are human-derived cell lines.

Specifically, *in vivo* daily oral dosing with the compound 166 resulted in significant anti-tumor activity in a broad range of human and mouse models as explained in the following passage taken from paragraph 760 of the application,

[0760] *In vivo* daily oral dosing of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one resulted in significant anti-tumor activity in a broad range of human and murine tumor models. Established tumor xenografts of prostate, colon, ovarian and hematologically-derived cancer cells have all demonstrated responsiveness to treatment in a dose-dependent manner, with ED₅₀s ranging from 4-65 mg/kg/d. The *in vivo* activity ranges from growth inhibition to stable disease and tumor regressions. For example, the compound induces regression and growth inhibition in subcutaneous KM12L4a human colon tumor xenografts in *nu/nu* mice. FIG. 1 shows tumor volume over time at various doses of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one. Dosing started when tumor xenografts reached 125 mm³. The results show significant tumor growth inhibition after 4 doses of greater than or equal to 30 mg/kg, and tumor regressions at 60 and 100 mg/kg. Similar results were observed in 90-100% of animals with larger KM12L4a colon tumor xenografts. Treatment started when tumor size reached 500 and 1000 mm³. Tissue concentration studies showed that 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was retained in the tumor with levels up to 65-300 fold higher than plasma at 24 hours after dosing. In addition, target modulation studies showed inhibition was maintained for more than 24 hours.

Further evidence of the *in vivo* anti-cancer therapeutic properties of the compounds of the invention as illustrated by compound 166 of the present application is described in paragraph 761 and shown in Figure 12. MV4-11 tumor cells were implanted in the flank of irradiated SCID-NOD mice. Tumors were then allowed to grow to 300, 500, or 1000 mm³ before treatment was initiated with daily oral dosing at 30 mg/kg/day. The compound corresponding to Example 109 of the present application displayed an ED₅₀ of 4 mg/kg/day in this tumor model in SCID-NOD mice, and a dose of 30 mg/kg/day inhibited the growth of larger MV4-11 tumors by 86% for tumors of 500 mm³ volume at start of treatment and by 80% for tumors of 1000 mm³ volume at start of treatment. Several complete regressions were also observed. Regressions were found to be stable after cessation of dosing. In those tumors that recurred, a second cycle of 30 mg/kg/day dosing of the compound again caused partial regression, indicating a lack of acquired resistance to the compound.

In a tumor metastasis study in which 4T1 murine breast tumor cells were implanted subcutaneously in BALB/c mice, compound 166 of the present application inhibited the primary tumor up to 82% and inhibited liver metastasis by more than 75% at all doses above 10 mg/kg/day as described in paragraph 762.

The present application also discloses evidence of the anti-angiogenic effects of inventive compounds. Figure 2 shows the results of an *in vivo* bFGF driven murine matrigel model of neovascularization. The bFGF supplement induces blood vessel formation (neovascularization or angiogenesis) that can be quantified by measuring the hemoglobin levels in the matrigel plugs following their removal from the animals. In these studies, mice were first implanted with the matrigel plug containing the bFGF and then orally dosed for 8 days with varying amounts of 4-amino-5-fluoro-3-[5-(4-methylpiperazinyl-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one, a compound representative of those disclosed in the present application (Example 109 of the present application). The plugs were then removed, and the hemoglobin concentrations were measured. As shown in Figure 2, significant inhibition of angiogenesis was observed, with an ED₅₀ of 3 mg/kg/day (ED₅₀ is defined as the dose that effectively inhibits angiogenesis by approximately 50%). Furthermore, all doses were well tolerated by the animals in the 8-day studies. Additional evidence of an anti-angiogenic effect is presented in Figure 10, which shows inhibition by 4-amino-5-fluoro-3-[5-(4-methylpiperazinyl-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in an *ex vivo* rat aortic ring assay.

As still further evidence of the guidance provided in the present application, Applicants direct the Examiner's attention to paragraph 441 of the application where it is noted that compounds of the invention can also be administered in conjunction with other anti-cancer drugs. Confirmatory evidence of the synergistic effect of compounds of the invention with other anti-cancer drugs is presented at paragraph 766 which describes studies using cytotoxic agents such as CPT-11 (Irinotecan) and 5-FU in combination with compound 166 in the KM12L4a colon and other tumor models. As described in paragraph 766, and shown in Figures 5-8,

Combination therapy studies were done using the standard cytotoxics, irinotecan and 5-FU, in the KM12L4a colon tumor model. Significant potentiation of activity was seen, with the most dramatic effects at low, inactive doses of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one as shown in FIG. 5. A cyclic dosing regimen of the compound at 50 mg/kg in combination with irinotecan gave excellent results, with 3 complete regressions and 7 partial regressions, as shown in FIG. 6. Synergistic and greater than

additive effects were also seen with trastuzumab combined with 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one in the erbB2-overexpressing ovarian tumor model, SKOV3ip1 (see FIG. 7). Additionally, tumor responses and regressions were significantly improved over each single agent treatment in the A431 epidermoid tumor model when 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one was combined with ZD1839 (Iressa) (see FIG. 8). These data suggest that 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one has the potential to be a broadly applicable and effective therapy for solid and hematological cancers.

Further, Applicant draws the Examiner's attention to three references submitted herewith describing *in vivo* studies on compound 166. This compound, which is the subject of claims 43, 83, and 89, is currently undergoing Phase II clinical trials after undergoing separate Phase I clinical trials for multiple myeloma (MM) and acute myelogenous leukemia (AML), as well as one for mixed solid tumors. The three references show tumor regression and in-vivo target modulation of receptor tyrosine kinases in colon cancer, MM, and AML cells. Particularly, in MV4;11 tumors, target modulation of pFLT3, pSTAT5 and pERK was achieved with compound 166, and tumor regressions and eradication of AML cells from bone marrow were shown in s.c. and bone marrow engraftment leukemic xenograft models. Clin Cancer Res 2005;11 (14) p.5281-91. In a separate colon cancer study, immunohistochemical analysis showed reduction of phosphorylated PDGFB and pERK in tumor cells after oral dosing of the compound 166, accompanied by a decreased tumor cell proliferation rate and reduced intratumoral microvessel density. Clin. Cancer Research 2005;11 (10) p.3633-41. Finally, in primary myeloma cells from t(4;14) patients, compound 166 inhibited downstream extracellular signal-regulated kinase phosphorylation and further displayed therapeutic efficacy in a xenograft mouse model of FGFR3 MM. Blood. 2005;105 p.2941-48.

As explained above, the Wands factors regarding enablement clearly support enablement of the amended and new claims presented herein. In view of the breadth of the claims being commensurate with Applicant's disclosure, the focused nature of the invention, the high level of skill in the art (as admitted by the Examiner on p. 8 of the Office Action), the relatively

predictable nature of the claimed subject matter as evidence by numerous publications, the extensive guidance of the working examples and other disclosure, Applicants respectfully submit that the full scope of the invention is enabled, including new claims 69-92. Accordingly, Applicants respectfully requests withdrawal of this ground of rejection. Should the Examiner maintain that the claimed methods are somehow not enabled, it is respectfully requested that specific supporting evidence be made of record.

II. Rejections Under 35 U.S.C. § 102

Applicants traverse the rejections of claims 42, 43 and 52 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent Nos. 6,605,617 and 6,800,760, and under 35 U.S.C. § 102(a) as allegedly being anticipated by U.S. Patent No. 6,605,617, WO 2002/0107392 and WO 200222895. Applicants note that the Examiner clarified that the latter two references cited in the 102(a) rejection should be U.S. Patent Application Publication No. 2002/0107392 and WO 2002/22598; Applicants will respond accordingly. Because none of the references teach each and every element of the claims, Applicants submit that claims 42, 43, 52 and new claims 69-92 are not anticipated by the cited references.

Applicants respectfully submit that none of the cited references teach any of the selected kinases recited in, for example, claim 42. Instead, each of the cited references discloses only that VEGFR1, VEGFR2 and bFGFR may be inhibited by the compounds disclosed therein. Moreover, the cited references do not fairly suggest Applicants' specific selection of receptor tyrosine kinases and cytoplasmic tyrosine kinases. As shown in the attached documents, there are at least 58 known human receptor tyrosine kinases distributed across 20 sub-families (*see*, EC 2.7.10.1, listed at, e.g., <http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.10.1>, a copy of which is submitted herewith for the convenience of the Examiner), and at least 32 known human cytoplasmic tyrosine kinases distributed across ten families (*see*, EC 2.7.10.2, listed at, e.g., <http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.10.2>, a copy of which is submitted herewith for the convenience of the Examiner). Thus, applicants have selected only a fraction of the at least 90 known tyrosine kinases. Likewise, none of the cited references teach or suggest the particular

cancers mediated by the claimed tyrosine kinases and thus do not teach or suggest the types of cancer recited in claims 86-91. Therefore, Applicants respectfully submit that claims 42, 43, 52 and new claims 69-92 are novel over the cited references, and respectfully request that these grounds of rejection be withdrawn.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. If any issues remain to be addressed in view of the present amendment and reply, the Examiner is requested to call the undersigned at the telephone number provided herein so that a prompt disposition of the application can be achieved.

Respectfully submitted,

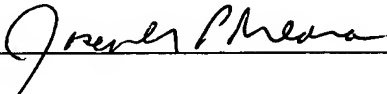
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